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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/115,963	07/15/1998	MICHEL SCHNEIDER	1201-52	2005

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HARTLEY, MICHAEL G

ART UNIT	PAPER NUMBER
1616	24

DATE MAILED: 02/07/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/115,963	SCHNEIDER ET AL.
Examiner	Art Unit	
Michael G. Hartley	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 25 October 2001.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-3,7,13-22,26 and 30-48 is/are pending in the application.
 - 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) Claim(s) ____ is/are allowed.
- 6) Claim(s) 1-3, 7, 13-22, 26 and 30-48 is/are rejected.
- 7) Claim(s) ____ is/are objected to.
- 8) Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on ____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on ____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All
 - b) Some *
 - c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. ____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
 - a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) <input type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). ____ .
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>23,25</u> .	6) <input type="checkbox"/> Other: ____ .

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Response to Amendment

The amendment filed 10/25/2000 has been entered. Applicant asserts that claims 6 and 25 are still pending because their cancellation was incorrectly included. However, once a claim has been cancelled, it cannot be reinstated. The directions to cancel claims 6 and 25 were specifically provided by applicant in the amendment filed 12/7/2000. Therefore, these claims were canceled and cannot be simply reinstated. Thus, claims 6 and 25 are no longer pending in the application.

Effective Priority Date

The effective filing date of the instant claims is still considered January 23, 1992, for the reasons set forth in the office action mailed 9/29/1999 (and reiterated in the office action mailed 8/29/2000).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-3, 7, 13-22, 26 and 30-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Quay (US 5,393,524), for the reasons set forth in the office action mailed 4/25/2001.

Claims 1-3, 7, 13-22, 26 and 30-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Glajch (US 5,147,631), for the reasons set forth in the office action mailed 4/25/2001.

Claims 1-3, 7, 13-22, 26 and 30-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cerny (US 4,957,656) and Ryan (US 4,900,540) in view of Glajch (US 5,147,631), Quay (US 5,393,524) and Tickner (4,265,251) in further view of the Dupont Technical Bulletin, for the reasons set forth in the office action mailed 4/25/2001.

Response to Arguments

Applicant's arguments filed 10/25/2001 have been fully considered but they are not persuasive.

Applicant asserts that there is no proper combination of the cited references, which disclose or suggest the limitations of a fluorinated gas that is bounded by a stabilizing layer of one or more phospholipids in lamellar form.

This is not found persuasive because Quay teaches that various shell materials may be employed to encapsulate the gas in the microvesicles, including phospholipids, denatured albumin, etc., see columns 7-8, which are the same materials as set forth in the instant claims. Quay also discloses that the gas is a fluorinated gas as claimed, see Table II, column 14. Glajch and Cerny also teach the combination of phospholipids and/or albumin, and modified to encapsulate a fluorinated gas, as set forth in the previous office action. Additionally the cited references teach that various shell materials are known to be useful for gas-microspheres as contrast agents for ultrasound imaging. The cited references also teach that various gases are known to be useful therein in an equivalent manner, including fluorinated gases, as claimed.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, all the cited art relates to ultrasound contrast agent comprising gas-filled microparticles. All the cited prior art teach that various gases may be used as equivalents to other known gases, e.g., Quay, Glajch and Tickner teaches that fluorinated gases may be used in such contrast agents in an equivalent manner to the gases used by Cerny and Ryan. One of ordinary skill in the art would have recognized that various equivalent gases, such as, fluorinated gases as taught by Quay, Glajch and Tickner could be used in such gas-filled microparticulate contrast agents, given that the prior art teach that a variety of gases may be employed. Clearly, Quay, Glajch and

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Tickner provide a teaching that fluorinated gases are useful for gas-filled contrast agent, (e.g., for ultrasound imaging), including various shell microbubbles, such as, those disclosed by Cerny, Ryan, and Quay which are similar to those claimed.

Applicant asserts that since the prior art teaches that their microbubbles do not have any problems, there is no reason to modify them.

This is not found persuasive because such an argument does not rebut an obviousness rejection under 35 USC 103 because while the prior art e.g., while Cerny may not have realized any need to improve at the time, another reference may still provide a teaching of improving thereon. For example, the cited art teaches that the use of fluorinated gases is an improvement to the gases employed by Cerny and Ryan.

Applicant asserts that the microbubbles disclosed by Ryan would include both a liquid and a gas.

The relevance of this argument is not seen. First, Ryan specifically teaches that the liposomes may encapsulate a gas. Also, the instant claims do not exclude any liquid from the microvesicles, e.g., the claims recite a "gas/liquid interface."

Applicant asserts that Glajch fails to teach that the fluorinated gases disclosed therein may be used in other types of microbubbles.

This is not found persuasive because Glajch teaches that fluorinated gases are known to be useful as the gas in ultrasound contrast agents and may be used in an equivalent manner to other known gases. One of ordinary skill in the art would have seen that such gases are improved gases, in which the improvement would be applicable to other ultrasound contrast agents.

Applicant asserts that Quay teaches away from using phospholipid or albumin microbubbles.

This is not found persuasive because Quay clearly teaches that such shell materials may be employed. Quay also teaches that various shell materials may be employed to encapsulate the gas in the microvesicles, including phospholipids, denatured albumin, etc., see columns 7-8. Disclosed examples and preferred embodiments do not constitute a teaching which is away from a broader disclosure or nonpreferred embodiments. *In re Susi*, 169 USPQ 423 (CCPA 1971), e.g., a known or obvious

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composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." *In re Gurley*, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994).

Applicant asserts that Tickner does not teach the use of various microbubbles, only saccharide compositions, thus teaches away from the instant invention.

This is not found persuasive because Tickner is relied upon to teach that the use of Freon as a gas, which may be used in an equivalent manner to other known gases, is known in the art of ultrasound contrast agents. Also, Tickner teaches that the term "microbubble" as used herein refers to bubbles which generate ultrasound signal on their formation.

Applicant asserts that the mere fact that the prior art may be modified does not make the modification obvious unless there is a desirability to make the modification.

Clearly, such desirability exists here. Quay, Glajch and Tickner teach that fluorinated gases are useful for gas containing microparticles for ultrasound imaging. Also, the prior art teaches that various gas-containing microparticles are useful for ultrasound imaging, which may contain various gases as equivalents. Some of the gases taught by Cerny and Ryan and Quay, Glajch and Tickner overlap. Clearly, the use of a fluorinated gas for ultrasound contrast agents is known, as taught by Quay, Glajch and Tickner. One of ordinary skill in the art would have been motivated to use this equivalent and known gas as the gas in such contrast agents, as well as equivalent shell materials, such as those disclosed by Cerny, Ryan, Quay, etc.

Applicant asserts that the modification cannot change the principle of operation of a reference.

The substitution of one known and equivalent gas for another, given the art teaches that various gases may be used in an equivalent manner does not change the principle of the operation. Further, changing the type of material to encapsulate the gas does not change the principle of operation. The principle of operation in ultrasound contrast agents is trapped gas, which have a greater echogenicity than the solid and liquid tissue surroundings. Clearly, Cerny, Ryan, Quay, Glajch and Tickner show that various shell materials and gases may be used in an equivalent manner to obtain the principle of entrapping gas, without changing any principles of operation.

Applicant asserts that there is no reasonable expectation of success.

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This is not found persuasive because there would have been a reasonable expectation of substituting one gas for another. This is shown by the fact that Cerny, Ryan, Quay, Glajch and Tickner teach the use of various gases and various shell materials, some of which overlap.

Applicant asserts unexpected results.

The unexpected results are not found persuasive. The results provided are not commensurate in scope with the either microbubbles or the gases as claimed. The data fails to show a trend for the scope of the claimed microvesicles which employ various distinct shell materials, e.g., albumins, phospholipids, etc, and various distinct gases. Also, the data does not show a direct comparison between the closest prior art, e.g., the microparticles disclosed by Cerny, Ryan, Quay, Glajch and Tickner.

The declaration under 37 CFR 1.132 filed 10/25/2001 is sufficient to overcome the rejection of claims 1-3, 7, 13-22, 26 and 30-48 based upon Hillman.

Conclusion

No claims are allowed at this time.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael G. Hartley whose telephone number is (703) 308-4411. The examiner can normally be reached on M-F, 7:30-5, off alternative Mondays. If attempts to reach the examiner by

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telephone are unsuccessful, the examiner's supervisor, Jose G. Dees can be reached on (703) 308-4628. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.



Michael G. Hartley
Primary Examiner
Art Unit 1616

MH

February 6, 2002